REMARKS

Applicant respectfully requests entry of the Amendment and reconsideration of the claims.

Claims 1-7, 9-12, 15-16, 18-24, 29-34, 36-40, 42, 44-46, 48-54, 59-66, 68-74, 76, 81-85, 90-96, 98-99, 108, 112, 129, and 130 are withdrawn as nonelected species claims. Applicants request rejoinder and further search of the subject matter of these claims upon notice of allowable subject matter of the elected species claims.

Claims 105-111, 121-123, and 126-127 have been amended and the amendments are supported throughout the specification including at page 5, lines 26-30; page 7, lines 5-9 and page 163, line 22 to page 164, line 4.

Priority

The Examiner contends that provisional applications 60/441,059 filed 1/16/2003, 60/488,610 filed July 18, 2003, and 60/510,314 filed October 8, 2003 do not provide support for a CDRH3 phage coat protein fusion comprising a "N terminal portion of about 1 to 4 amino acids in which some or all amino acid positions are structural" and a "C terminal portion of about 1 to 6 amino acids in which some or all amino acid positions are structural". Applicants respectfully disagree with the Examiner and request acknowledgement of the claim for priority of the currently pending claims.

Applicants contend that the provisional applications fully support the claimed subject matter throughout the specifications. Several examples of support from the provisional applications are provided herein. For example, Applicants direct the Examiner's attention to:

> At page 18 of the provisional 60/441,059 (filed January 16, 2003) where it states:
>
> "In one embodiment, structural amino acid positions in a CDRH3 are typically located near the N and C terminus of the CDRH3. Structural amino acid positions are selected from the group consisting of the first N-terminal amino acid, the second N-terminal amino acid and **at least one of the last 6 amino acids at the C-terminus of a heavy chain CDRH3**. In another embodiment, at least one structural amino acid position is one or both of the first two amino acid positions at the N-terminus of a heavy chain CDRH3. In another embodiment, **said at least one structural amino acid position is a third and/or fourth amino acid position from the C-terminus**."
>
> At page 21:
> "A library of randomly generated 17 amino acid CDRH3 indicated that a consensus sequence R-L-R at the N-terminus may be preferred for some embodiments."

At page 58 of the provisional:

"A scaffold can then be prepared by limiting the diversity at the structural amino acid positions in a particular scaffold and inserting a loop of amino acids between those structural positions ranging from 1 to 20 amino acids, preferably 5-15 amino acids and more preferably 10 to 12 amino acids. The loop of amino acids can be randomized if desired.

The invention also provides for 1) *polypeptides comprising a CDRH3 region as a fusion polypeptide;"*

The examples indicate that a fusion protein with p3 viral coat protein was prepared at page 99:

"Vectors encoding fusion polypeptides comprising variant CDRs were constructed as follows. In general, vectors for antibody phage display were constructed by modifying vector pS1602 (Sidhu et al., J. Mol. Biol. (2000), 296:487-495). *Vector pS1602, which has pTac promoter sequence and malE secretion signal sequence, contained a sequence of human growth hormone fused to the C-terminal domain of the gene-3 minor coat protein (p3). The sequence encoding hGH was removed, and the resulting vector sequence served as the vector backbone for construction of vectors of the present invention that contain DNA fragments encoding the Llama anti-HCG antibody* (Spinelli, S., Frenken, L., Bourgeois, D., de Ron, L., Bos, W., Verris, T., Anguille, C., Cambilau, C., Tegoni, M., (1996) *Nat. Struct. Biol*. 3(9), 752-757)."

The examples indicate at page 107:

"Finally, we combined the above two analysis, positional and by residue type, to determine those amino acids and those positions which were significantly over represented (Figure 45). Positions 96(Arg), 97(Leu), 99(Arg),102a (Gly), 102b (Gly), **102e(Trp), 102f(Phe), 102h(Val), and 102j (Val)** show a significant deviation from random (one and a half standard deviations or greater) for both preference of amino acid type at that position and bias for that position for any given residue as compared to the distribution of that amino acid along the entire 17 residue loop. These amino acid preferences indicate that certain amino acids are preferred at these positions, and that these positions are more likely to play a structural role in CDRH3."

Applicants submit that these passages as well as figures 45 and 46 provide for support and priority for claim 105. It is clear that the specification of the priority document describes a CDRH3 phage coat protein fusion protein (see italics) comprising a " N terminal portion of about 1 to 4 amino acids in which some or all amino acid positions are structural". Please see underlined sections above and Figures 45 and 46. It is also clear that the specification of the

priority document also describes and supports a "C terminal portion of about 1 to 6 amino acids in which some or all of the amino acid positions are structural". See bold sections above. Applicants respectfully request acknowledgement of priority of the currently pending claims to provisional application 60/441,059 filed January 16, 2003.

Moreover, similar support can be found in the provisional application 60/488,610 filed July 18, 2003. For example,

At page 18 of the provisional, the application states:

"In one embodiment, structural amino acid positions in a CDRH3 are located near the N and C terminus of the CDRH3. For example, in a 17 amino acid CDRH3 region, structural amino acid positions are selected from the group consisting of the first N-terminal amino acid, the second N-terminal amino acid, **at least one of the last 6 amino acids at the C-terminus of a heavy chain CDRH3 or mixtures thereof.** In another embodiment, at least one structural amino acid position is one or both of the first two amino acid positions at the N-terminus of a heavy chain CDRH3. In another embodiment, **said at least one structural amino acid position is a third , fourth and/or sixth amino acid position from the C-terminus."**

At page 22,

"Another embodiment of a CDRH3 region comprises an amino acid sequence R-L/I/M-A_3-R-$(A_5)_n$, wherein A_3 and A_5 are any naturally occurring amino acid and n is 1 to 20. A library of randomly generated 17 amino acid CDRH3 indicated that a consensus sequence R-L/I/M- A_3-R at the N-terminus may be preferred for some embodiments."

At page 109,

"Amino acids that deviated most significantly from random ($p<0.05$) showed a strong selection bias for particular amino acids at certain positions in the CDRH3 peptide. The N terminal end of the peptide was biased towards the sequence motif R(L/I/M)XR. Near the central portion of the peptide, the preference seemed to be for either glycine or hydrophilic residues. The C-terminal end of CDR3 (positions 102e-102j) was characterized by an over representation of hydrophobes (Phe, Val, Ile and Trp) at particular positions."

At page 113,

"These results indicate that amino acids located at the N and C-terminus of CDRH3 should be less diversified than other amino acids. Structural amino acid positions were identified as those positions that had a ratio of wild type amino acid to alanine of at least about 3 to 1 or greater and more preferably, about 10 to 1 or greater. The structural amino acid positions identified in the analysis include the first two N-terminal amino acid positions (positions 96 and 97 in this

example) and **one or more of the last 6 amino acid positions located at the C-terminus in the 17 amino acid peptide of CDRH3 (positions 102e, 102f, 102g, 102h, 102i and 102j)**."

Applicants submit that these passages as well as figure 45 provide for support and priority for claim 105. It is clear that the specification of the priority document describes a CDRH3 phage coat protein fusion protein comprising an "N terminal portion of about 1 to 4 amino acids in which some or all amino acid positions are structural". Please see underlined sections above and Figure 45. It is also clear that the specification of the priority document also describes and supports a "C terminal portion of about 1 to 6 amino acids in which some or all of the amino acid positions are structural". See bold sections above. Applicants request acknowledgement of priority of the currently pending claims to provisional application 60/488,610 filed July 18, 2003.

Rejection under 35 U.S.C. § 102(a)

The Examiner rejects claims 105-107, 109, 111, 113 and 115-128 under 35 U.S.C. § 102(a) as allegedly being anticipated by Bond et al. (*J. Mol. Biol.*, 332:643-655 (2003)). Applicant respectfully traverses this rejection.

Applicants submit that the Bond et al paper was published on September 19, 2003, and is therefore not properly considered prior art to the instant application. (Copy of journal listing attached) Applicants submit that the currently pending claims are entitled to a priority date of at least Jan. 16, 2003, and since Bond et al. was published after that date, it is not properly considered prior art.

Applicant respectfully requests removal of the rejections under 35 U.S.C. § 102(a).

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 105-107, 109-111, 113 and 115-128 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description for allegedly new matter. Applicants respectfully traverse.

The examiner contends that a ***fusion*** protein comprising a CDRH3 scaffold having a " N terminal portion of about 1 to 4 amino acids in which some or all of the amino acids are structural" and "C terminal portion of about 1-6 amino acids in which some or all amino acid positions are structural." is new matter. Applicants disagree.

As indicated above, applicants contend that not only the instant application but the provisional applications provide support for the claimed subject matter. The passages cited in the section concerning priority are relevant here and are incorporated by reference herein. Exemplary passages of the instant specification, Appl. No. 10/759,731, are provided below:

At page 7,

"For example, in a 17 amino acid CDRH3 region, structural amino acid positions are selected from the group consisting of the first N-terminal amino acid, the second N-terminal amino acid, **at least one of the last 6 amino acids at the C-terminus of a heavy chain CDRH3 or mixtures thereof.** The central portion has a length of 9 amino acids that can vary in sequence. In another embodiment, at least one structural amino acid position is one or both of the first two amino acid positions at the N-terminus of a heavy chain CDRH3. **In another embodiment, said at least one structural amino acid position is a third , fourth and/or sixth amino acid position counting from the C-terminus."**

At page 7,

"The length of the N terminal flanking region, central portion, and C-terminal flanking region is determined by selecting the length of CDRH3, randomizing each position and identifying the structural amino acid positions at the N and C-terminal ends of the CDRH3. The length of the N and C terminal flanking sequences should be long enough to include at least one structural amino acid position in each flanking sequence. In some embodiments, the length of the N-terminal flanking region is at least about from 1 to 4 contiguous amino acids, the central portion of at least one non-structural position(s) can vary from about 1 to 20 contiguous amino acids, and **the C-terminal portion is at least about from 1 to 6 contiguous amino acids**."

At page 11,

"The invention also provides for *1) fusion polypeptides; 2) fusion polypeptides to viral coat proteins or portions thereof;* 3) polynucleotides encoding any of the polypeptides; 4) replicable expression vectors comprising a polynucleotide encoding the polypeptides of the invention; 5) host cells comprising the vectors; 6) a library comprising a plurality of vectors of the invention and 7) a population of variant polypeptides or polynucleotides of the invention."

At page 14,

"A library of randomly generated 17 amino acid CDRH3 indicated that a consensus sequence R-L/I/M- A_3-R at the N-terminus may be preferred for some embodiments."

At page 15,

"In one embodiment, the scaffold has a N terminal sequence of R-L/I/M-A_3-R, wherein A_3 is any naturally occurring amino acid. In another embodiment, the N terminal sequence is R-I-A_3-C, wherein A_3 is any naturally occurring amino acid. In other embodiments, the N terminal sequence comprises R-I, L-L,V-L, or R-L. In some embodiments, **the C terminus has a sequence of CWVTW. In other embodiments the C-terminal sequence comprises F-X-R-V, W-X-X-L, W-X-M-P, or W-V, wherein X can be any naturally occurring amino acid**."

At page 150,

"Amino acids that deviated most significantly from random ($p<0.05$) showed a strong selection bias for particular amino acids at certain positions in the CDRH3 peptide. The N terminal end of the peptide was biased towards the sequence motif R(L/I/M)XR. Near the central portion of the peptide, the preference seemed to be for either glycine or hydrophilic residues. **The C-terminal end of CDR3 (positions 100g-102) was characterized by an over representation of hydrophobes (Phe, Val, Ile and Trp) at particular positions.**"

At page 153,

"The structural amino acid positions identified in the analysis include the first two N-terminal amino acid positions (positions 96 and 97 in this example) and **one or more of the last 6 amino acid positions located at the C-terminus in the 17 amino acid peptide of CDRH3** (positions 100g, 100h, 100i, 100j, 101 and 102)."

Thus, applicants submit that the claims are supported and described in the instant application as well at least the provisional applications 60/441,059 filed January 16, 2003 and 60/488,610 filed July 18, 2003. Applicants request withdrawal of the rejection on this basis.

35 USC§ 112, 2nd para

The examiner rejected claims 123- 127 under 35 USC§ 112, 2nd para. The examiner has contends some of the language of the claims is indefinite. Applicants traverse.

The examiner raised concerns regarding the terms "variant amino acid" and "the binding polypeptide" in claim 123. While not acquiescing to the rejection and solely to expedite prosecution, claim 123 has been amended to delete these terms, rendering this rejection moot.

The examiner raised concerns regarding the term "variants thereof" in claim 127. While not acquiescing to the rejection and solely to expedite prosecution, claim 127 has been amended to delete this term, rendering this rejection moot. The examiner raised concerns regarding the term "pV1" in claim 127. Applicants have corrected this inadvertent typographical error.

Withdrawal of the rejection is respectfully requested.

Rejection under Obviousness-Type Double Patenting

The Examiner rejects claims 105, 107, 109, 111, 113, 115-122 and 127-128 under the judicially created doctrine of obviousness-type double patenting over claims 22, 25, 26, 30-31, 35-37 and 48-50 of copending Application No. 11/102,502 in view of Sidhu et al. (*J. Mol. Biol.*, 296:487-495 (2000)) and evidence by Bond et al. (*J. Mol. Biol.*, 332:643-655 (2003)). Applicant acknowledges the Examiner's rejection for obviousness-type double patenting and requests that this rejection be held in abeyance until notice of allowable subject matter.

Summary

Applicant submits that the claims of the present application are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicant's representative at the telephone number listed below, if the Examiner believes that doing so will advance prosecution.

Please charge any additional fees or credit any overpayment to Merchant & Gould P.C., Deposit Account No. 13-2725.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Date: May 29 2008

Katherine M. Kowalchyk
Reg. No. 36,848
KMK:BRD:sab

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